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EXAMINER	
SAKELARIS, SALLY A	
ART UNIT	PAPER NUMBER
1634	

DATE MAILED: 08/12/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/888,320	BARRY ET AL.	
	Examiner	Art Unit	
	Sally A Sakelaris	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on 5/28/2003

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-5,8-12,21,22,25,28,29 and 34-48* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-5, 8-12, 21, 22, 25, 28, 29 and 34-48* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

This action is in response to Applicant's amendment and response received 5/28/2003 in response to the first action on the merits mailed 11/20/2002. Claims 1-5, 8-12, 21, 22, 25, 28, 29 and 34-48 are now pending, Claims 6, 7, 23, 24, 26, and 27 have been previously cancelled, claims 13-15, 17-20, and 30-33 have been withdrawn as drawn to non-elected inventions, claim 16 is cancelled herein, and claims 34-48 have been added herein. Applicant's amendments and arguments have been thoroughly reviewed, but are not persuasive for the reasons that follow. All rejections not reiterated herein are hereby withdrawn. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action. This action is **Final**.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

1. Claims 1-5, 8-12, 21, 22, 25, 28, and 29 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for methods of determining the ability of a *Mycobacterium tuberculosis* bacterium to oxidize a thioamide or a thiocarbonyl found in the drugs ethionamide(ETA), thiacetazone(TA), and thiocarlide(TC), said method comprising detecting a mutation(from the table below *) in an EtaA gene of said bacterium, wherein detection of the mutation(from the table below*) is indicative of decreased ability to oxidize a thioamide or thiocarbonyl found in the drugs ETA(thioamide), TA(thioamide), and

TC(thiocarbonyl), does not reasonably provide enablement for methods of determining the ability of a *M. tuberculosis* bacterium to oxidize any thioamide or any thiocarbonyl, said method comprising detecting any mutation in the EtaA gene in said bacterium, wherein detection of the mutation is indicative of decreased ability to oxidize any thioamide or any thiocarbonyl. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

The following factors have been considered in formulating this rejection (*In re Wands*, 858F.2d 731, 8 USPQ2d 1400 (Fed. Cir. 1988): the breadth of the claims, the predictability or unpredictability of the art, the amount of direction or guidance presented, the presence or absence of working examples of the invention and the quantity of experimentation necessary.

*Table

Nucleotide position of frameshift mutations/ Related Drug(s) with decreased oxidative ability	Amino Acid position of SNP/ Related Drug(s) with decreased oxidative ability
Δ 1 nt 65 / ETA, TA, TC	G43→C / ETA, TA, TC
+ 1 nt 811 / ETA, TA, TC	P51→L / ETA, TA, TC
	D58→A / ETA, TA, TC
	Y84→D / ETA, TA, TC
	T342→K / ETA, TA
	A381→P / ETA, TA, TC

Claims 1-5, 8-12, 21, 22, 25, 28, and 29 are broadly drawn to methods of determining the ability of a *M. tuberculosis* bacterium to oxidize any thioamide or any thiocarbonyl, said method comprising detecting any mutation in the EtaA gene in said bacterium, wherein detection of the mutation is indicative of decreased ability to oxidize any thioamide or any thiocarbonyl. The specification teaches a series of mutations, those listed above in the table, that have been found to be associated with conferring drug resistance. The specification further teaches a study involving 3 such thioamide/thiocarbonyl-containing antituberculosis medications; ETA, TA, and TC. The specification teaches that the mutations, listed in the table, resulted in the bacterium's inability to oxidize the thioamide/thiocarbonyl within the drug and consequently, the mutations conferred a drug-resistance to the bacterium. The specification also teaches the low rate at which the *M. tuberculosis*(MTb) bacterium experiences "synonymous" mutations; that is MTb rarely has random mutation that do not affect the gene sufficiently so that the enzyme encoded by the gene has reduced ability to activate a thioamide prodrug(Specification Page 12). The specification teaches in Figure 4C that one strain in particular with a mutation was conferred with drug susceptibility instead of resistance. The specification on Page 8 teaches that ETA includes a thioamide, thioacetazone includes a thioamide, and thiocarlide includes a thiocarbonyl. Page 9, [25] teaches that all three, ETA, thiacetazone and thiocarlide all represent thioamide drugs. Page 12 [37] teaches ETA, thiacetazone, and thiocarlide to be thioamide drugs. Lastly, page 28 [85] teaches that ETA, thiacetazone, and thiocarlide as examples of thiocarbonyl-containing drugs.

The specification does not teach that every mutation in the EtaA gene confers a drug-resistance to the bacterium as a result of its inability to oxidize a thioamide or a thiocarbonyl

group. For example, the specification omits a teaching of a mutation in every nucleic acid of the EtaA gene that is associated with resistance to all of the drugs in both of the claimed drug classes. The specification also does not teach the way in which each drug, ETA, TA, or TC differs; nor does it teach the characteristic shared between all drugs responsible for conferring the antibiotic resistance. Also omitted, is the exact class of drugs to which each of the three belong, and what structural motif they have that is responsible for this classification. The specification does not teach the other mutations in the EtaA gene that would be indicative of either the drug-resistant phenotype, or the drug-sensitive phenotype(ie mutations in every nucleotide are not taught to be correlated). The specification further omits any teaching of a common property represented within each mutation that is responsible for the resulting drug resistance because of the inability to oxidize the thiocarbonyl groups. Additionally, the specification teaches that the drugs, ETA and TA and TC confer different resistance status to the bacterium(Fig 4C). The specification does not teach how or why such supposedly similar thioamide or thiocarbonyl-containing antituberculosis medications confer varying degrees, if at all, of drug resistance. As stated in *Vaek* (20 USPQ2d 1438), the specification must teach those of skill in the art how to make and how to use the invention as *broadly* as it is claimed" (emphasis added). The amount of guidance needed to enable the invention is related to the amount of knowledge in the state of the art as well as the predictability in the art. *In re Fisher* 427 F. 2d 833, 839, 166 USPQ 18, 24 (CCPA 1970). Predictability or lack thereof in the art refers to the ability of one of skill in the art to extrapolate the disclosed or known results to the invention that is claimed. If one of skill in the art can readily anticipate the effect of a change in the subject matter to which the claimed invention is directed, then there is predictability in the

art. On the other hand, if one skilled in the art cannot readily anticipate the effect of a change in the subject matter to which the claimed invention is directed, then there is unpredictability in the art. With respect to the present invention, what other mutations may exist in addition to those listed in Figure 4C and additionally which methods could be used predictably to determine the presence of these mutations. Furthermore, one cannot readily anticipate which of the mutations within the gene(i.e. mutations other than those set forth in Table 4C) actually result in the inability to oxidize thiocarbonyl groups and that would be associated with a patient that is resistant to such thiocarbonyl-containing antituberculosis medications, as opposed to those frameshifts or polymorphisms that result in drug sensitivity. The prior art, incorporated by reference, of Sreevatsan et al. teach that Mtb "has an extremely low rate of synonymous mutations, that is, that the organism has few, if any, random mutations which do not have a functional effect" applicant should note that the reference does not teach a correlation between the occurrence of amino acid change and specific drug resistances. While it is clear from the prior art and specification that the vast majority of Mtb mutations result in amino acid substitutions, it is not taught that all of the amino acid changes result in functional changes that all confer drug resistance to all thioamide and thiocarbonyl drugs. The Sreevatsan reference teaches in their words, a "strong suspicion that the variation has functional consequences, such as antibiotic resistance"(Sreevatsan, 9872). However, the reference provides no data relating the amino acid changes to any antibiotic resistance. It is further noted that "greater than 95% of nucleotide substitutions cause amino acid replacements..."(Pg. 9870), but again, no data correlating the amino acid changes and a specific antibiotic resistance is taught. Additionally, applicants have not shown that "every mutation in the EtaA gene will reduce the ability of a Mtb

organism to oxidize a thioamide or thiocarbonyl drug, and therefore increase resistance of the organism"(Pg. 14). Thereby, the scope of the claims do not bear a reasonable correlation to the scope of enablement provided by the specification and undue experimentation would be required to practice the full scope of the claims because this would require randomized searching of mutations in the entire EtaA gene that would cause an oxidation deficiency. While the specification provides results regarding the presence of mutations listed in the table on page 5 of this office action, the specification has not taught an association between these mutations and the actual effect they have on the bacterium's ability to oxidize and therefore on its potential for resistance. Such random trial by error experimentation is considered to be undue and in view of the high level of unpredictability in the art and the lack of guidance provided in the specification, undue experimentation would be required for one of skill in the art to practice the invention as it is broadly claimed.

Therefore, the specification does not provide the guidance necessary to distinguish between mutations that are associated with oxidative capabilities and mutations or polymorphisms that are not associated with conferring either resistance or sensitivity to drugs as a result of their oxidative capacity. In view of the high level of unpredictability in the art and the lack of guidance provided in the specification, undue experimentation would be required for one of skill in the art to practice the invention as it is broadly claimed.

Response to Arguments: "C"

1. **The rejection is based on a misunderstanding of the invention and on a misreading of the specification's data.**

Applicant asserts that the action "fundamentally misunderstands the invention and misreads the data presented"(Pg. 11). With respect to Figure 4C, Applicant's attention is directed to Strain AS7TAR(7^{th} down) where the mutation at nucleotide 1025 results in the amino acid change of T342-K. The examiner's intention in her reference to Figure 4C, was to point out only the uncertainty that exists in the teaching of a mutation in the EtaA gene conferring an amino acid change that confers a resistance to ETA(L) but not to another thiocarbonyl-containing antituberculosis medication, thiocarlide(S). This finding in Figure 4C is considered to be unpredictable considering applicant's assertion that "organisms with mutations in the EtaA gene are resistant to thioamide and thiocarbonyl drugs, while those with the unmutated, wild type gene are susceptible to them"(Pg.11). Here, in Figure 4C, there exists a teaching of a mutation existing that does not also confer resistance to all thioamines and thiocarbonyls(esp. thiocarlide) drugs. Applicant should note that the examiner understands the invention as claimed.

2. **The rejection is based in part on a series of 5 incorrect statements to the effect that the specification does not teach that mutations in the EtaA gene are correlated with resistance to thioamide and thiocarbonyl drugs**

In response to (i) and (iv), while examiner concedes that Sreevatsan et al. teach that Mtb "has an extremely low rate of synonymous mutations, that is, that the organism has few, if any, random mutations which do not have a functional effect" applicant should note that the reference does not teach a correlation between the occurrence of amino acid change and specific drug resistances. While it is clear from the prior art and specification that the vast majority of Mtb mutations result in amino acid substitutions, it is not taught that all of the amino acid changes result in functional changes that all confer drug resistance to all thioamide and thiocarbonyl

drugs. The Sreevatsan reference teaches in their words, a "strong suspicion that the variation has functional consequences, such as antibiotic resistance"(Sreevatsan, 9872). However, the reference provides no data relating the amino acid changes to any antibiotic resistance. It is further noted that "greater than 95% of nucleotide substitutions cause amino acid replacements..."(Pg. 9870), but again, no data correlating the amino acid changes and a specific antibiotic resistance is taught. Additionally, applicants have not shown that "every mutation in the EtaA gene will reduce the ability of a Mtb organism to oxidize a thioamide or thiocarbonyl drug, and therefore increase resistance of the organism"(Pg. 14). For example, applicants have not taught that mutations that could occur in nucleotides 1, 2, 3, ... 1143, etc all confer the claimed drug resistance.

In response to (ii), (iii), and (v) the examiner maintains that a common property represented by the drugs that is responsible for the shared resistant phenotype is not taught by the specification as originally filed or included in a 132 declaration. The specification teaches only that "we postulate that ETA is activated via the corresponding S-oxide (2) to a sulfinate that can form an analogous aldehyde equivalent..."(Pg. 29). The specification asserts only that, "thiacetazone and thiocarlide that might be similarly activated by EtaA-catalyzed S-oxidation"(Pg. 28). It is further unpredictable that the specification refers to thiacetazone and thiocarlide in some parts as thioamide drugs(Pg. 9 line 8) and in other parts as thiocarbonyls(Pg. 28 line 11). The specification should clearly assert the exact mechanism by which each of the claimed drugs metabolize the mutant EtaA gene product and in doing so, asserting the common thread shared by all drug classes. It is presently highly unpredictable to assume that all drugs in

both of these claimed classes share the same mechanism and as a result the same conferred resistance.

In response to "c", although examiner could not locate the preceeding "b" in applicant's response, the examiner maintains that a mutation in the EtaA gene is not necessarily correlated with resistance to all thioamide and thiocarbonyl drugs. Applicant's attention is directed back to Figure 4C where a mutation in the EtaA gene is correlated with a low-level resistance to "ETA" and "TA" but to a susceptibility to "TC"(7^{th} strain in list). It should be noted that even more unpredictability exists in claiming resistance to the entire drug classes, than already exists to this one drug, "TC".

In response to "d", please see above response to (i) and (iv).

In response to "e", examiner maintains that while the specific quote was objected to by applicant, the DeBarber reference corroborates the unpredictability that exists in the claimed invention as it lacks the teachings required as referred to in the above responses.

In response to "f", *Wands* factors 1 thru 8, applicant is directed to the standing enablement rejection above.

With respect to new claims 34-48, Claims 34-48 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for methods of determining the ability of a *Mycobacterium tuberculosis* bacterium to oxidize a thioamide or a thiocarbonyl found in the drugs ethionamide(ETA), thiacetazone(TA), and thiocarlide(TC), said method comprising detecting a mutation(from the table below *) in an EtaA gene of said bacterium, wherein detection of the mutation(from the table below*) is indicative of decreased ability to oxidize a

thioamide or thiocarbonyl found in the drugs ETA(thioamide), TA(thioamide), and TC(thiocarbonyl), does not reasonably provide enablement for said method comprising detecting any mutation in the EtaA gene in said bacterium, wherein detection of the mutation is indicative of decreased ability to oxidize one of ETA(thioamide), TA(thioamide), or TC(thiocarbonyl),. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

The following factors have been considered in formulating this rejection (*In re Wands,* 858F.2d 731, 8 USPQ2d 1400 (Fed. Cir. 1988): the breadth of the claims, the predictability or unpredictability of the art, the amount of direction or guidance presented, the presence or absence of working examples of the invention and the quantity of experimentation necessary.

Claims 34-48 are broadly drawn to methods of determining the ability of a *M. tuberculosis* bacterium to oxidize one of ETA(thioamide), TA(thioamide), or TC(thiocarbonyl), said method comprising detecting any mutation in the EtaA gene in said bacterium, wherein detection of the mutation is indicative of decreased ability to oxidize one of ETA(thioamide), TA(thioamide), or TC(thiocarbonyl), The specification teaches a series of mutations, those listed above in the table, that have been found to be associated with conferring drug resistance. The specification further teaches a study involving 3 such thioamide/thiocarbonyl-containing antituberculosis medications; ETA, TA, and TC. The specification teaches that the mutations, listed in the table, resulted in the bacterium's inability to oxidize the thioamide/thiocarbonyl within the drug and consequently, the mutations conferred a drug-resistance to the bacterium. The specification also teaches the low rate at which the *M. tuberculosis*(MTb) bacterium experiences "synonymous" mutations; that is MTb rarely has random mutation that do not affect

the gene sufficiently so that the enzyme encoded by the gene has reduced ability to activate a thioamide prodrug(Specification Page 12). The specification teaches in Figure 4C that one strain in particular with a mutation was conferred with drug susceptibility instead of resistance. The specification on Page 8 teaches that ETA includes a thioamide, thioacetazone includes a thioamide, and thiocarlide includes a thiocarbonyl. Page 9, [25] teaches that all three, ETA, thiacetazone and thiocarlide all represent thioamide drugs. Page 12 [37] teaches ETA, thiacetazone, and thiocarlide to be thioamide drugs. Lastly, page 28 [85] teaches that ETA, thiacetazone, and thiocarlide as examples of thiocarbonyl-containing drugs.

The specification does not teach that every mutation in the EtaA gene confers a drug-resistance to the bacterium as a result of its inability to oxidize a thioamide or a thiocarbonyl group. For example, the specification omits a teaching of a mutation in every nucleic acid of the EtaA gene that is associated with resistance to all of the drugs in both of the claimed drug classes. The specification also does not teach the way in which each drug, ETA, TA, or TC differs; nor does it teach the characteristic shared between all drugs responsible for conferring the antibiotic resistance. Also omitted, is the exact class of drugs to which each of the three belong, and what structural motif they have that is responsible for this classification. The specification does not teach the other mutations in the EtaA gene that would be indicative of either the drug-resistant phenotype, or the drug-sensitive phenotype(ie mutations in every nucleotide are not taught to be correlated). The specification further omits any teaching of a common property represented within each mutation that is responsible for the resulting drug resistance because of the inability to oxidize the thiocarbonyl groups. Additionally, the specification teaches that the drugs, ETA and TA and TC confer different resistance status to the

bacterium(Fig 4C). The specification does not teach how or why such supposedly similar thioamide or thiocarbonyl-containing antituberculosis medications confer varying degrees, if at all, of drug resistance. As stated in *Vaek* (20 USPQ2d 1438), the specification must teach those of skill in the art how to make and how to use the invention as *broadly* as it is claimed" (emphasis added). The amount of guidance needed to enable the invention is related to the amount of knowledge in the state of the art as well as the predictability in the art. *In re Fisher* 427 F. 2d 833, 839, 166 USPQ 18, 24 (CCPA 1970). Predictability or lack thereof in the art refers to the ability of one of skill in the art to extrapolate the disclosed or known results to the invention that is claimed. If one of skill in the art can readily anticipate the effect of a change in the subject matter to which the claimed invention is directed, then there is predictability in the art. On the other hand, if one skilled in the art cannot readily anticipate the effect of a change in the subject matter to which the claimed invention is directed, then there is unpredictability in the art. With respect to the present invention, what other mutations may exist in addition to those listed in Figure 4C and additionally which methods could be used predictably to determine the presence of these mutations. Furthermore, one cannot readily anticipate which of the mutations within the gene(i.e. mutations other than those set forth in Table 4C) actually result in the inability to oxidize thiocarbonyl groups and that would be associated with a patient that is resistant to such thiocarbonyl-containing antituberculosis medications, as opposed to those frameshifts or polymorphisms that result in drug sensitivity. The prior art, incorporated by reference, of Sreevatsan et al. teach that Mtb "has an extremely low rate of synonymous mutations, that is, that the organism has few, if any, random mutations which do not have a functional effect" applicant should note that the reference does not teach a correlation between

the occurrence of amino acid change and specific drug resistances. While it is clear from the prior art and specification that the vast majority of Mtb mutations result in amino acid substitutions, it is not taught that all of the amino acid changes result in functional changes that all confer drug resistance to all thioamide and thiocarbonyl drugs. The Sreevatsan reference teaches in their words, a "strong suspicion that the variation has functional consequences, such as antibiotic resistance"(Sreevatsan, 9872). However, the reference provides no data relating the amino acid changes to any antibiotic resistance. It is further noted that "greater than 95% of nucleotide substitutions cause amino acid replacements..."(Pg. 9870), but again, no data correlating the amino acid changes and a specific antibiotic resistance is taught. Additionally, applicants have not shown that "every mutation in the EtaA gene will reduce the ability of a Mtb organism to oxidize a thioamide or thiocarbonyl drug, and therefore increase resistance of the organism"(Pg. 14). Thereby, the scope of the claims do not bear a reasonable correlation to the scope of enablement provided by the specification and undue experimentation would be required to practice the full scope of the claims because this would require randomized searching of mutations in the entire EtaA gene that would cause an oxidation deficiency. While the specification provides results regarding the presence of mutations listed in the table on page 5 of this office action, the specification has not taught an association between these mutations and the actual effect they have on the bacterium's ability to oxidize and therefore on its potential for resistance. Such random trial by error experimentation is considered to be undue and in view of the high level of unpredictability in the art and the lack of guidance provided in the specification, undue experimentation would be required for one of skill in the art to practice the invention as it is broadly claimed.

Therefore, the specification does not provide the guidance necessary to distinguish between mutations that are associated with oxidative capabilities and mutations or polymorphisms that are not associated with conferring either resistance or sensitivity to drugs as a result of their oxidative capacity. In view of the high level of unpredictability in the art and the lack of guidance provided in the specification, undue experimentation would be required for one of skill in the art to practice the invention as it is broadly claimed.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

2. Claims 25 and 46 are rejected under 35 U.S.C. 103(a) as being unpatentable over Badcock et al in view of Philipp et al and in further view of Ahern et al.

Badcock et al. teach the EtaA gene of *Mycobacterium tuberculosis* and its probable function as a monooxygenase(See CDS nt position 14983..16452 of Accession # Z83864)

Badcock et al. do not teach a kit containing primers to amplify an EtaA gene.

However, Philipp et al. teach an integrated map of the genome of the tubercle bacillus, *Mycobacterium tuberculosis* H37Rv, and comparison with *Mycobacterium leprae*. The reference further teaches that the "goal of such a study was to elucidate the genomic organization of *Mycobacterium tuberculosis* and to establish a set of ordered DNA fragments, a valuable

genetic resource"(Philipp, Pg. 3137). The reference further teaches that "several recent examples leading to the identification of genes involved in drug resistance or encoding new therapeutic targets testify to the power of the approach." Furthermore, the reference teaches the use of PCR amplification using primers specific to the *Mycobacterium tuberculosis* sequence of genomic DNA in order to facilitate gene mapping, data handling and analysis(Pg. 3133).

However, Ahern et al. teaches the use of kits in "some tasks such as constructing genomic libraries, designing primer sets, or synthesizing nucleic acids"(The Scientist, 1995), for the expected benefit of buying premade reagents and kits are convenient and they save time.

Therefore it would have been obvious to one skilled in the art at the time the invention was made to use the kit concept of Ahern et al, to have encompassed the EtaA gene sequence and motivation provided by Philipp et al. and monooxygenase function as provided by Badcock et al. to make a kit containing primers for amplifying an EtaA gene of *Mycobacterium tuberculosis* bacterium.

Response to Arguments:

In response to "F", applicant is directed to the motivation provided by Philipp et al. who teaches that the "goal of such a study was to elucidate the genomic organization of *Mycobacterium tuberculosis* and to establish a set of ordered DNA fragments, a valuable genetic resource"(Philipp, Pg. 3137). The reference further teaches that "several recent examples leading to the identification of genes involved in drug resistance or encoding new therapeutic targets testify to the power of the approach." Furthermore, the reference teaches the use of PCR amplification using primers specific to the *Mycobacterium tuberculosis* sequence of genomic

DNA in order to facilitate gene mapping, data handling and analysis(Pg. 3133). The examiner maintains that a motivation to combine references thus exists.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communication from the examiner should be directed to Sally Sakelaris whose telephone number is (703) 306-0284. The examiner can normally be reached on Monday-Friday from 8:00AM-5:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, W.Gary Jones, can be reached on (703)308-1152. The fax number for the Technology Center is (703)305-3014 or (703)305-4242.

Any inquiry of a general nature or relating to the status of this application should be directed to Chantai Dessau whose telephone number is (703)605-1237.

Sally Sakelaris

August 11, 2003

CARLA J. MYERS
PRIMARY EXAMINER